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Examiner: Phillip Gambel **Group:** 1644

Date: November 13, 2006

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OFFICIAL
RG 11/13/06

From: Deirdre E. Sanders, Esq.

Subject: **Docket No.:** 0975.1005-017
Applicants: Junming Le *et al.*
Application No.: 10/043,432
Filing Date: January 10, 2002

Number of pages including this cover sheet: 26

Dear Examiner Gambel,

Please officially file the following attached documents in the above-referenced application:

- Supplemental Information Disclosure Statement
- PTO-1449
- Claim copies from 4 Non-Published Applications

Best regards,

Deirdre E. Sanders

DES/CMW/atc
November 13, 2006

PATENT APPLICATION
DOCKET NO.: 0975 1005-017

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel

Application No.: 10/043,432 Group Art Unit: 1644

Filed: January 10, 2002 Examiner: Phillip Gambel

Confirmation No.: 3288

OFFICIAL

Title: A METHOD OF TREATING CACHEXIA WITH ANTI-TNF ANTIBODIES

PG 11/13/06

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

November 13, 2006 Christine M. Wise
Date Signature

Christine M. Wise
Typed or printed name of person signing certificate

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Information Disclosure Statement is submitted:

[ ] under 37 CFR 1.129(a), or
(First/Second submission after Final Rejection)

[ ] under 37 CFR 1.97(b), or
(Within any one of the following time periods: three months of filing national application (other than a CPA) or date of entry of the national stage in an international application, or before the mailing date of a first office action on the merits in a non-provisional application, including a CPA, or a Request for Continued Examination).

[ ] under 37 CFR 1.97(c) together with either:

[ ] a Statement under 37 CFR 1.97(e), as checked below, or

[ ] a $180.00 fee under 37 CFR 1.17(p), or
(After the 37 CFR 1.97(b) time period, but before final action or notice of allowance, whichever occurs first)

[ ] under 37 CFR 1.97(d) together with:

[ ] a Statement under 37 CFR 1.97(e), as checked below, and

[ ] a $180.00 fee under 37 CFR 1.17(p), or
(Filed after final action or notice of allowance, whichever occurs first, but on or before payment of the issue fee)

[X] under 37 CFR 1.97(i):
Applicant requests that the IDS and cited reference(s) be placed in the application file.

Statement Under 37 CFR 1.97(e)

[ ] Each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement; or

[ ] No item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

Statement Under 37 CFR 1.704(d) (Patent Term Adjustment)
Applies to original applications (other than design) filed on or after May 29, 2000

[ ] Each item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart application and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the Information Disclosure Statement.

[X] Enclosed herewith is form PTO-1449:

[ ] Copies of the cited references are enclosed.

[X] Copies of issued U.S. patents and published U.S. applications are not required and are not being provided.

[ ] Copies of the cited references are enclosed except those entered in prior application, U.S. Application No. [ ], to which priority under 35 U.S.C. 120 is claimed. [The earlier application contains copies of the cited references.]

[ ] The listed references were cited in the enclosed International Search Report in a counterpart foreign application.

[ ] The "concise explanation" requirement (non-English references) for reference(s) [ ] under 37 CFR 1.98(a)(3) is satisfied by:

[ ] the explanation provided on the attached sheet.

[ ] the explanation provided in the Specification.

[ ] submission of the enclosed International Search Report.

[ ] submission of the enclosed English-language version of a foreign Search Report and/or foreign Office Action.

[ ] the enclosed English language abstract.

[X] Applicant requests that the following pending published applications be considered:

Examiner's Initials

___ U.S. Patent Application No. 10/319,011, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel, filed December 12, 2002, Docket No.: 0975.1005-029.

___ U.S. Patent Application No. 10/371,443, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel, filed February 21, 2003, Docket No.: 0975.1005-031.

___ U.S. Patent Application No. 10/371,961, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel, filed February 21, 2003, Docket No.: 0975.1005-033.

___ U.S. Patent Application No. 10/665,971, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel, filed September 19, 2003, Docket No.: 0975.1005-036.

___ U.S. Patent Application No. 10/774,118, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel, filed February 6, 2004, Docket No.: 0975.1005-038.

___ U.S. Patent Application No. 11/053,749, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight, Scott Siegel and Bernard Scallon, filed February 7, 2005, Docket No.: 0975.1005-040.

___ U.S. Patent Application No. 11/195,589, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel, filed August 2, 2005, Docket No.: 0975.1005-042.

___ U.S. Patent Application No. 11/010,954, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight, Scott Siegel and David Shealy, filed December 13, 2004, Docket No.: 0975.1005-043.

___ U.S. Patent Application No. 11/053,750, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight, Scott Siegel and Bernard Scallon, filed February 7, 2005, Docket No.: 0975.1005-045.

___ U.S. Patent Application No. 10/957,134, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel, filed September 30, 2004, Docket No.: 0975.1005-048.

___ U.S. Patent Application No. 11/170,753, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel, filed June 29, 2005, Docket No.: 0975.1005-050.

___ U.S. Patent Application No. 11/297,655, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel, filed December 8, 2005.

___ U.S. Patent Application No. 11/314,941, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David M. Knight and Scott Siegel, filed December 20, 2005, Docket No.: 0975.1005-059.

___ U.S. Patent Application No. 11/400,787, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel, filed April 7, 2006, Docket No.: 0975.1005-062.

[X] Applicant requests that the following pending non-published applications be considered:

___ U.S. Patent Application No. 11/143,926 by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel, filed June 2, 2005, Docket No.: 0975.1005-052.

___ U.S. Patent Application No. 11/401,391, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David M. Knight and Scott Siegel, filed April 10, 2006.

___ U.S. Patent Application No. 11/501,162, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel, filed August 8, 2006.

___ U.S. Patent Application No. 11/582,153, by Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and Scott Siegel, filed October 16, 2006.

_____ _____

Examiner Date

[X] A copy of each above-cited non-published application, including the current claims, is enclosed, except any application filed on or after June 30, 2003, which has been scanned into the PTO's Image File Wrapper (IFW) system and is available to the examiner. However, copies of the claims for the non-published applications are enclosed.

[ ] A copy of each above-cited application, including the current claims, is enclosed, except those entered in prior application, U.S. Application No. [ ], to which priority under 35 U.S.C. 120 is claimed.

The Examiner is requested to return a copy of the above list of pending applications indicating which references were considered with the next office communication.

It is requested that the information disclosed herein be made of record in this application.

Method of payment:

[ ] A check for the fee noted above is enclosed, or the fee has been included in the check with the accompanying Reply. A copy of this Statement is enclosed.

[ ] Please charge Deposit Account 08-0380 in the amount of $[ ].

[X] Please charge any deficiency in fees and credit any overpayment to Deposit Account 08-0380.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Deirdre E. Sanders

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Concord, MA 01742-9133
Dated:

iManage 655391_1.DOC
DES/CMW/kaf

Claims for 11/143,926

What is claimed is:

1. An anti-TNFα antibody antigen-binding fragment comprising a human constant region wherein said antigen-binding fragment (i) competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNFα and (ii) binds to a neutralizing epitope of human TNFα with an affinity of at least 1×10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

2. The fragment of Claim 1, selected from the group consisting of : Fab, Fab', $F(ab')_2$, Fv, a monomer, a dimer, a single chain antibody, and a single chain antibody fragment.

3. The fragment of Claim 1, comprising a single heavy chain, a heavy chain constant region, a heavy chain joining region, a heavy chain diversity region, a heavy chain variable region, a single light chain, a light chain constant region, a light chain joining region and a light chain variable region.

4. The fragment of Claim 1, comprising an chimeric H chain comprising an antigen binding region derived from the H chain of a non-human antibody specific for TNFα, which is linked to at least a portion of a human H chain C region.

5. The fragment of Claim 3 which is a heavy chain variable region or light chain variable region and which binds a portion of a TNFα and neutralizes TNFα activation of procoagulant activity of endothelial cells.

6. An anti-TNFα chimeric antibody fragment which comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5.

7. The fragment of Claim 6, wherein the non-human variable region is murine.

8. The fragment of Claim 6, wherein the non-human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 4.

9. The fragment of Claim 1, which is produced recombinantly.

10. The fragment of Claim 1, wherein the fragment is of immunoglobulin class IgG1, IgG2, IgG3, IgG4 or IgM.

11. The fragment of Claim 4, wherein the portion of the human H chain C region is CH_1 or CH_2.

NONPUBLISHED IDS REFERENCE DO NOT SCAN

USSN 11/401,391 Claims

What is claimed is:

1. A method of treating a TNFα-mediated seronegative arthropathy in a human in need thereof, comprising administering to the human an effective TNFα-inhibiting amount of an anti-TNFα antibody or antigen-binding fragment thereof, said antibody comprising a human constant region, wherein said anti-TNFα antibody or antigen-binding fragment thereof (i) competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNFα and (ii) binds to a neutralizing epitope of human TNFα with an affinity of at least 1×10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

2. The method of Claim 1, wherein the antibody or antigen-binding fragment comprises a human constant region and a human variable region.

3. The method of Claim 1, which comprises at least one human light chain and at least one human heavy chain.

4. The method of Claim 3, wherein the light chain comprises all antigen-binding regions of the light chain of A2 (ATCC Accession No. PTA-7045).

5. The method of Claim 3, wherein the heavy chain comprises all antigen-binding regions of the heavy chain of A2 (ATCC Accession No. PTA-7045).

6. The method of Claim 3, wherein the light chain comprises all antigen-binding

regions of the light chain of A2 (ATCC Accession No. PTA-7045) and the heavy chain comprises all antigen-binding regions of the heavy chain of A2 (ATCC Accession No. PTA-7045).

7. The method of Claim 1, wherein the anti-TNFα antibody or antigen-binding fragment thereof is of immunoglobulin class IgG1, IgG2, IgG3, IgG4 or IgM.

8. The method of Claim 1, wherein the anti-TNFα antigen-binding fragment thereof is selected from the group consisting of Fab, Fab', $F(ab')_2$ and Fv.

9. The method of Claim 1, wherein said analysis comprises labelling the anti-TNFα antibody or antigen-binding fragment thereof and measuring direct binding of ^{125}I labelled anti-TNFα antibody or antigen-binding fragment thereof to immobilized rhTNFα, and wherein said antibodies are labelled to a specific activity of about 9.7 μCi/μg by the iodogen method.

10. The method of Claim 1, wherein the antigen-binding Fab fragment of an anti-TNFα antibody is administered to the human by means of intramuscular administration.

11. The method of Claim 1, wherein said TNFα-inhibiting amount of the anti-TNFα antibody or antigen-binding fragment comprises a single or divided dose of about 0.1 - 50 mg/kg.

12. The method of Claim 11, wherein the single or divided dose is selected from the group consisting of: about a 0.1 - 1 mg/kg dose, about a 1.0 - 5 mg/kg dose, about a 5 - 10 mg/kg dose and about a 10 - 20 mg/kg dose.

13. The method of Claim 11, wherein the single or divided dose is about a 5 - 20

mg/kg dose.

14. The method of Claim 1, further comprising administering to the human an amount of an anti-inflammatory agent effective to treat the TNFα-mediated seronegative arthropathy.

15. The method of Claim 14, wherein the anti-inflammatory agent is selected from the group consisting of: pentasa, mesalazine, asacol, codeine phosphate, benorylate, fenbufen, naprosyn, diclofenac, etodolac, indomethacin, aspirin and ibuprofen.

16. The method of Claim 1, further comprising administering to the human an effective amount of an anti-pain agent to treat pain associated with the TNFα-mediated seronegative arthropathy.

17. The method of Claim 1, further comprising administering to the human an amount of methotrexate effective to treat the TNFα-mediated seronegative arthropathy.

18. The method of Claim 1,wherein a composition comprising the antibody or antigen-binding fragment and a pharmaceutically acceptable carrier is administered.

19. The method of Claim 1 wherein the antibody or antigen-binding fragment has specificity for a neutralizing epitope of human TNF-α.

20. A method of treating a TNFα-mediated seronegative arthropathy in a human in need thereof, comprising administering to the human an effective TNFα-inhibiting amount of an anti-TNFα antibody or antigen-binding fragment thereof (i) comprises the antigen-binding regions of A2 (ATCC Accession No. PTA-7045), and (ii) binds to a neutralizing epitope of human TNF-α with an affinity of

at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

21. A method of treating a TNFα-mediated seronegative arthropathy in a human in need thereof, comprising administering to the human an effective TNFα-inhibiting amount of an anti-TNFα antibody or antigen-binding fragment thereof, said antibody comprising a human IgG1 constant region, and wherein said antibody or antigen-binding fragment (i) competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNF-α, and (ii) binds to a neutralizing epitope of human TNF-α with an affinity of at least 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

22. A method of treating a TNFα-mediated seronegative arthropathy in a human in need thereof, comprising administering to the human an effective TNFα-inhibiting amount of an anti-TNF-α antibody or antigen-binding fragment thereof, said antibody comprising a human IgG1 constant region, wherein said antibody or antigen-binding fragment (i) comprises the antigen-binding regions of A2 (ATCC Accession No. PTA-7045), and (ii) binds to a neutralizing epitope of human TNF-α with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

23. A method of treating a TNFα-mediated seronegative arthropathy in a human in need thereof, comprising administering to the human an effective TNFα-inhibiting amount of a light chain that specifically binds human TNFα and competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNF-α, said light chain comprising a human light chain constant region and a human light chain framework region, wherein said human light chain binds to a neutralizing epitope of human TNF-α with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard

analysis.

24. A method of treating a TNFα-mediated seronegative arthropathy in a human in need thereof, comprising administering to the human an effective TNFα-inhibiting amount of a heavy chain that specifically binds human TNFα and competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNF-α, said heavy chain comprising a human heavy chain constant region and a human heavy chain framework region, wherein said heavy chain binds to a neutralizing epitope of human TNF-α with an affinity of at least 1×10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

25. The method of Claim 22, wherein the antibody or antigen-binding fragment comprises a human constant region and a human variable region.

26. The method of Claim 22, wherein the antibody or antigen-binding fragment comprises at least one human light chain and at least one human heavy chain.

27. The method of Claim 26, wherein the light chain comprises all antigen-binding regions of the light chain of A2 (ATCC Accession No. PTA-7045).

28. The method of Claim 26, wherein the heavy chain comprises all antigen-binding regions of the heavy chain of A2 (ATCC Accession No. PTA-7045).

29. The method of Claim 26, wherein the light chain comprises all antigen-binding regions of the light chain of A2 (ATCC Accession No. PTA-7045) and the heavy chain comprises all antigen-binding regions of the heavy chain of A2 (ATCC Accession No. PTA-7045).

30. The method of Claim 22, wherein a composition comprising the antibody or antigen-binding fragment and a pharmaceutically acceptable carrier is administered.

31. The method of Claim1, wherein the human has psoriatic arthritis.

USSN 11/501,162 Claims

What is claimed is:

1. A method of treating TNFα-mediated hepatitis C in a human in need thereof, comprising administering to the human a therapeutically effective TNFα-inhibiting amount of an anti-TNFα antibody for a sufficient period of time to treat the hepatitis C, wherein said anti-TNFα antibody competitively inhibits binding of monoclonal antibody A2 or chimeric monoclonal antibody cA2 to TNFα, and wherein said anti-TNFα antibody binds to a neutralizing epitope of TNFα *in vivo* with an affinity of at least 1×10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

2. The method of Claim 1, wherein said anti-TNFα antibody competitively inhibits binding of TNFα to chimeric monoclonal antibody cA2.

3. The method of Claim 1, wherein said anti-TNFα antibody is chimeric monoclonal antibody cA2, or a TNFα binding fragment thereof.

4. A method of treating TNFα-mediated endometriosis in a human in need thereof, comprising administering to the human a therapeutically effective TNFα-inhibiting amount of an anti-TNFα antibody for a sufficient period of time to treat the endometriosis, wherein said anti-TNFα antibody competitively inhibits binding of monoclonal antibody A2 or chimeric monoclonal antibody cA2 to TNFα, and wherein said anti-TNFα antibody binds to a neutralizing epitope of TNFα *in vivo* with an affinity of at least 1×10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

5. The method of Claim 4, wherein said anti-TNFα antibody competitively inhibits binding of TNFα to chimeric monoclonal antibody cA2.

6. The method of Claim 4, wherein said anti-TNFα antibody is chimeric monoclonal antibody cA2, or a TNFα binding fragment thereof.

7. A method of treating TNFα-mediated chronic obstructive pulmonary disease (COPD) in a human in need thereof, comprising administering to the human a therapeutically effective TNFα-inhibiting amount of an anti-TNFα antibody for a sufficient period of time to treat the COPD, wherein said anti-TNFα antibody competitively inhibits binding of monoclonal antibody A2 or chimeric monoclonal antibody cA2 to TNFα, and wherein said anti-TNFα antibody binds to a neutralizing epitope of TNFα *in vivo* with an affinity of at least 1×10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

8. The method of Claim 7, wherein said anti-TNFα antibody competitively inhibits binding of TNFα to chimeric monoclonal antibody cA2.

9. The method of Claim 7, wherein said anti-TNFα antibody is chimeric monoclonal antibody cA2, or a TNFα binding fragment thereof.

10. A method of treating TNFα-mediated congestive heart failure in a human in need thereof, comprising administering to the human a therapeutically effective TNFα-inhibiting amount of an anti-TNFα antibody for a sufficient period of time to treat the congestive heart failure, wherein said anti-TNFα antibody competitively inhibits binding of monoclonal antibody A2 or chimeric monoclonal antibody cA2 to TNFα, and wherein said anti-TNFα antibody binds to a neutralizing epitope of

TNFα *in vivo* with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

11. The method of Claim 10, wherein said anti-TNFα antibody competitively inhibits binding of TNFα to chimeric monoclonal antibody cA2.

12. The method of Claim 10, wherein said anti-TNFα antibody is chimeric monoclonal antibody cA2, or a TNFα binding fragment thereof.

13. A method of treating TNFα-mediated psoriatic arthritis in a human in need thereof, comprising administering to the human a therapeutically effective TNFα-inhibiting amount of an anti-TNFα antibody for a sufficient period of time to treat the psoriatic arthritis, wherein said anti-TNFα antibody competitively inhibits binding of monoclonal antibody A2 or chimeric monoclonal antibody cA2 to TNFα, and wherein said anti-TNFα antibody binds to a neutralizing epitope of TNFα *in vivo* with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

14. The method of Claim 13, wherein said anti-TNFα antibody competitively inhibits binding of TNFα to chimeric monoclonal antibody cA2.

15. The method of Claim 13, wherein said anti-TNFα antibody is chimeric monoclonal antibody cA2, or a TNFα binding fragment thereof.

16. A method of treating TNFα-mediated giant cell arteritis in a human in need thereof, comprising administering to the human a therapeutically effective TNFα-inhibiting amount of an anti-TNFα antibody for a sufficient period of time to treat the giant cell arteritis, wherein said anti-TNFα antibody competitively inhibits binding of monoclonal antibody A2 or chimeric monoclonal antibody cA2 to

TNFα, and wherein said anti-TNFα antibody binds to a neutralizing epitope of TNFα *in vivo* with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

17. The method of Claim 16, wherein said anti-TNFα antibody competitively inhibits binding of TNFα to chimeric monoclonal antibody cA2.

18. The method of Claim 16, wherein said anti-TNFα antibody is chimeric monoclonal antibody cA2, or a TNFα binding fragment thereof.

19. A method of treating TNFα-mediated transdermal ulcers in a human in need thereof, comprising administering to the human a therapeutically effective TNFα-inhibiting amount of an anti-TNFα antibody for a sufficient period of time to treat the transdermal ulcers, wherein said anti-TNFα antibody competitively inhibits binding of monoclonal antibody A2 or chimeric monoclonal antibody cA2 to TNFα, and wherein said anti-TNFα antibody binds to a neutralizing epitope of TNFα *in vivo* with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

20. The method of Claim 19, wherein said anti-TNFα antibody competitively inhibits binding of TNFα to chimeric monoclonal antibody cA2.

21. The method of Claim 19, wherein said anti-TNFα antibody is chimeric monoclonal antibody cA2, or a TNFα binding fragment thereof.

22. A method for treating a TNFα-mediated disease in a human in need thereof, comprising administering a therapeutically effective TNFα-inhibiting amount of an anti-TNFα antibody transdermally for a sufficient period of time to treat the TNFα-mediated disease, wherein said anti-TNFα antibody competitively inhibits

binding of monoclonal antibody A2 or chimeric monoclonal antibody cA2 to TNFα, and wherein said anti-TNFα antibody binds to a neutralizing epitope of TNFα *in vivo* with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

23. The method of Claim 22, wherein said anti-TNFα antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

24. The method of Claim 22, wherein said anti-TNFα antibody is monoclonal antibody cA2, or a TNF binding fragment thereof.

25. A method for treating a TNFα-mediated disease in a human in need thereof, comprising administering a therapeutically effective TNF-inhibiting amount of an anti-TNF antibody nasally for a sufficient period of time to treat the TNFα-mediated disease, wherein said anti-TNFα antibody competitively inhibits binding of A2 or cA2 to TNF, and wherein said anti-TNF antibody binds to a neutralizing epitope of TNF-α *in vivo* with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

26. The method of Claim 25, wherein said anti-TNFα antibody competitively inhibits binding of TNFα to chimeric monoclonal antibody cA2.

27. The method of Claim 25, wherein said anti-TNFα antibody is chimeric monoclonal antibody cA2, or a TNFα binding fragment thereof.

28. A method for treating a TNFα-mediated disease in a human in need thereof, comprising administering a therapeutically effective TNFα-inhibiting amount of an anti-TNFα antibody by pulmonary administration for a sufficient period of time to treat the TNFα-mediated disease, wherein said anti-TNFα antibody

competitively inhibits binding of monoclonal antibody A2 or chimeric monoclonal antibody cA2 to TNFα, and wherein said anti-TNFα antibody binds to a neutralizing epitope of TNFα *in vivo* with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

29. The method of Claim 28, wherein said anti-TNFα antibody competitively inhibits binding of TNFα to chimeric monoclonal antibody cA2.

30. The method of Claim 28, wherein said anti-TNFα antibody is chimeric monoclonal antibody cA2, or a TNFα binding fragment thereof.

31. A method for treating a TNFα-mediated disease in a human in need thereof, comprising administering a therapeutically effective TNFα-inhibiting amount of an anti-TNFα antibody by injection into a joint for a sufficient period of time to treat the TNFα-mediated disease, wherein said anti-TNFα antibody competitively inhibits binding of monoclonal antibody A2 or chimeric monoclonal antibody cA2 to TNFα, and wherein said anti-TNFα antibody binds to a neutralizing epitope of TNFα *in vivo* with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

32. The method of Claim 31, wherein said anti-TNFα antibody competitively inhibits binding of TNFα to chimeric monoclonal antibody cA2.

33. The method of Claim 31, wherein said anti-TNFα antibody is chimeric monoclonal antibody cA2, or a TNFα binding fragment thereof.

Claims for 11/582,153

What is claimed is:

1. A method of inhibiting TNFα in a human patient, wherein said human patient has a blood pathology, comprising administering to the human patient an effective TNFα-inhibiting amount of an anti-TNFα antibody or antigen-binding fragment thereof, said antibody comprising a human constant region, wherein said anti-TNFα antibody or antigen-binding fragment thereof (i) competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNFα and (ii) binds to a neutralizing epitope of human TNFα with an affinity of at least 1×10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

2. A method of inhibiting TNFα in a human patient, wherein said human patient has a blood pathology, comprising administering to the human patient an effective TNFα-inhibiting amount of an anti-TNFα antibody or antigen-binding fragment thereof, wherein said anti-TNFα antibody comprises a human IgG1 constant region and wherein said anti-TNFα antibody or antigen-binding fragment thereof (i) competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNFα and (ii) binds to a neutralizing epitope of human TNFα with an affinity of at least 1×10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

3. A method of inhibiting TNFα in a human patient, wherein said human patient has a blood pathology, comprising administering to the human patient an effective TNFα-inhibiting amount of an anti-TNFα chimeric antibody, wherein said anti-

TNFα chimeric antibody comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO.:3 and SEQ ID NO.:5.

4. A method of inhibiting TNFα in a human patient, wherein said human patient has a blood pathology, comprising administering to the human patient an effective TNFα-inhibiting amount of an anti-TNFα chimeric antibody, wherein said anti-TNFα chimeric antibody comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO.:3 and SEQ ID NO.:5 and an IgG1 human constant region.

5. The method of Claim 3 wherein the non human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO.:2 and SEQ ID NO.:4.

6. The method of Claim 4 wherein the non human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO.:2 and SEQ ID NO.: 4.

7. The method of Claim 1 wherein said anti-TNFα antibody is a humanized antibody.

8. The method of Claim 1 wherein said anti-TNFα antibody is a human antibody.

9. The method of Claim 1 wherein said anti-TNFα antibody is a chimeric antibody.

10. The method of Claim 1 wherein said anti-TNFα antibody is administered to the human by means of parenteral administration.

11. The method of Claim 1 wherein said anti-TNFα antibody is administered to the human by means of intravenous administration, subcutaneous administration or intramuscular administration.

12. The method of Claim 1 wherein said TNFα-inhibiting amount of said anti-TNFα antibody comprises a single or divided dose of about 0.1 - 50 mg/kg.

13. The method of Claim 12 wherein the single or divided dose is one selected from 0.5, 0.9, 1, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 mg/kg per day on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

14. The method of Claim 1, wherein said fragment is selected from the group consisting of Fab, Fab', $F(ab')_2$ and Fv.

15. The method of Claim 1, wherein said antibody or antigen-binding fragment comprises a human constant region and a human variable region.

16. The method of Claim 1, wherein said antibody or antigen-binding fragment comprises at least one human light chain and at least one human heavy chain.

17. The method of Claim 16, wherein the light chain comprises all antigen-binding regions of the light chain of A2 (ATCC Accession No. PTA-7045).

18. The method of Claim 16, wherein the heavy chain comprises all antigen-binding regions of the heavy chain of A2 (ATCC Accession No. PTA-7045).

19. The method of Claim 16, wherein the light chain comprises all antigen-binding regions of the light chain of A2 (ATCC Accession No. PTA-7045) and the heavy chain comprises all antigen-binding regions of the heavy chain of A2 (ATCC Accession No. PTA-7045).

20. A method of inhibiting TNFα in a human patient, wherein said human patient has a blood pathology, comprising administering to the human patient an anti-TNFα antibody or antigen-binding fragment thereof, said antibody comprising a human constant region, wherein said antibody or antigen-binding fragment (i) comprises the antigen-binding regions of A2 (ATCC Accession No. PTA-7045), and (ii) binds to a neutralizing epitope of human TNFα with an affinity of at least 1×10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

21. The method of Claim 1, further comprising administering a composition comprising the antibody or antigen-binding fragment of Claim 1 and a pharmaceutically acceptable carrier.

22. The method of Claim 1, wherein said antibody or antigen-binding fragment has specificity for a neutralizing epitope of human TNFα.

23. The antibody or antigen-binding fragment of Claim 1, wherein said Scatchard analysis comprises labeling the anti-TNFα antibody or antigen-binding fragment thereof and measuring direct binding of ^{125}I labeled anti-TNFα antibody or antigen-binding fragment thereof to immobilized rhTNFα, and wherein said

antibodies are labelled to a specific activity of about 9.7 μCi/μg by the iodogen method.

24. The method of Claim 1, wherein said blood pathology is anemia.

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INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION

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(Use several sheets if necessary)

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U.S. PATENT DOCUMENTS				
EXAMINER INITIAL	REF NO.	DOCUMENT NUMBER Number-Kind Code (if known)	ISSUE DATE / PUBLICATION DATE MM-DD-YYYY	NAME OF PATENTEE OR APPLICANT OF CITED DOCUMENT
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EXAMINER	DATE CONSIDERED